FORMULATION, PHYSICAL CHARACTERIZATION AND *IN VITRO* RELEASE STUDIES OF ACECLOFENAC ALGINATE BEADS PREPARED BY IONOTROPIC GELATION FOR SUSTAINED RELEASE

Dissertation work submitted to
THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY,
CHENNAI

In partial fulfillment of the award of degree of

MASTER OF PHARMACY
(Pharmaceutics)

Submitted by

G. THANUMALAIYAN

Under the guidance of
Mr.B. Rajalingam, M.pharm.,(Ph.D)
Assistant Professor

March 2009

DEPARTMENT OF PHARMACEUTICS
COLLEGE OF PHARMACY
SRI RAMAKRISHNA INSTITUTE OF PARAMEDICAL SCIENCES
COIMBATORE – 641044

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Certificate

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Dr. T.K. Ravi, M.Pharm., Ph.D., FAGE,
Principal,
College of Pharmacy,
S.R.I.P.M.S.,
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Mr. B. Rajalingam, M.Pharm.,(Ph.D.).,
Assitant Professor,
Department of Pharmaceutics,
College of Pharmacy,
S.R.I.P.M.S.,
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Dr. M. Gopal Rao, M.Pharm.,Ph.D.,
Head - Department of Pharmaceutics,
College of Pharmacy,
S.R.I.P.M.S.,
Coimbatore - 641 044.

Place: Coimbatore
Date:

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INTRODUCTION

With many drugs, the basic goal of therapy is to achieve a steady state blood or tissue level that is therapeutically effective and nontoxic for an extended period of time. The design of proper dosage regimen is an important element in accomplishing this goal. A basic objective in dosage form design is to optimize the delivery of medication so as to achieve a measure of control for the therapeutic effect in the face of uncertain fluctuations in the *in vivo* environment where the drug release takes place. This is usually accomplished by maximizing drug availability, i.e., by attempting to attain a maximum rate and extent of drug absorption, however, control of drug release through formulation also implies controlling bioavailability to reduce drug absorption rates.[1]

Sustained release (SR) systems are defined as "Any drug delivery system that achieves slow release of drug over an extended period of time if this system provides some control as spatial, temporal or both for drug releases in the body and it is considered as a sustained release system".

THE SUSTAINED RELEASE CONCEPT[1]

Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot, and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. In the case of orally administered forms, however, this period is measured in hours and critically depends on residence time of the dosage form in the gastrointestinal tract.

The goal in designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site action, reducing the dose required, or providing uniform drug delivery.

If one were to imagine the ideal drug delivery system, two prerequisites would be required. First, it would be a single dose for duration of treatment, whether it is for days or week, as in infections, or for lifetime of the patient, as in hypertension or diabetes. Second, it should deliver the active entity (drug) directly to the site of action, there by minimizing or eliminating side effects. This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body.[2]

It is obvious that this imaginary delivery system will have changing requirements for different disease states and different drugs. Thus, we wish to deliver the therapeutic agent to a specific site and for a specific time. In other words, the objective is to achieve both spatial and temporal placement of drug. Currently, it is possible to only achieve both of these goals, with most drug delivery systems. The given pictorial representation in **FIG:1** gives an idea about the sustained drug delivery system[3]

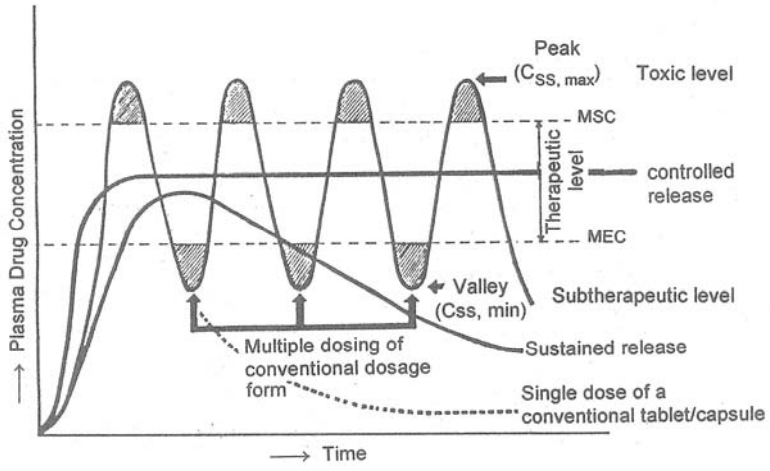


FIG: 1 Plasma Concentration Vs time profile

FACTORS GOVERNING THE DESIGN OF DOSAGE FORM[4]

There are number of factors which may influence the design of any dosage form. Similarly design of sustained release dosage form is governed by the factors listed below in **Table: 1**

Table:1 Factors governing the design of sustained release dosage form[3]

Drug related	Aqueous solubility Partition co-efficient Protein binding Molecular weight Drug stability
Pharmacokinetic	Absorption rate Elimination half life Rate of metabolism Dosage form index (DI) First pass metabolism
Pharmacodynamic	Therapeutic range Therapeutic index (TI) Plasma-concentration responses
Route of administration	Dose size Absorption efficiency Duration of action
Pharmacological	Changes in drug effect upon multiple dosing Sensitizing Tolerance
Physiological	Prolonged drug absorption Variability in GI emptying and motility GI blood flow

DRUGS SUITABLE FOR EXTENDED RELEASE FORMULATIONS[1]

Not all the drugs lend themselves to the formulation of an extended release product. The important factors that are to be considered in the choice of a drug as a candidate of SR preparations are given in **Table: 2**.

Table: 2 Characteristics of drugs unsuitable for peroral SR forms

Characteristics	Drugs
Not effectively absorbed in the lower intestine	Riboflavin, Ferrous salts
Absorbed and excreted rapidly, short biological half lives	Penicillin G,Furosemide
Long biological half lives (>12 hour)	Diazepam,Phenytoin
Large doses required (>1gm)	Sulfonamides
Cumulative action and undesirable side effects, drugs with low therapeutic index	Phenobarbitol,Digitoxin
Precise dosage titrates to individual is required	Anticoagulants, Cardiac glycosides
No clear advantage for SR formulation	Griseofulvin

ADVANTAGES OF SR DOSAGE FORM

- The frequency of drug administration will be reduced.
- Patient compliance can be improved.
- Drug administration can be made more convenient as well.
- The blood level oscillation characteristic of multiple dosing of conventional dosage forms are reduced, because more even blood level is maintained.

- The total amount of the drug administered can be reduced, thus maximizing availability with a minimum.
- The better control of drug absorption can be attained by reducing availability.
- The safety margin of high potency drugs can be increased, and the incidence of both local and systemic adverse side effects can be reduced.
- Overall, administration of sustained release forms enables increased reliability of therapy.

DISADVANTAGES OF SR DOSAGE FORM

- Administration of sustained release medication does not permit the prompt termination of therapy. Immediate changes in drug need during therapy, such as might be encountered if significant adverse effects are noted, cannot be accommodated.
- The physician has less flexibility in adjusting dosage regimens. This is fixed by the dosage form design.
- Sustained release forms are designed for the normal population, i.e., on the basis of average biological half lives. Consequently, disease state that alter drug disposition, significant variation, and so forth are not accommodated.
- Economic factors must also be assessed, since more costly processes and equipments are involved in manufacturing of many sustained release dosage forms.

MULTIPARTICULATE MODIFIED RELEASE SYSTEMS [5, 6]

Sustained - release solid dosage form systems are available either as single-unit (non divided) formulation or as multiple-unit (divided) formulation forms. The single-unit dosage forms usually refer to where the drug is dissolved or dispersed throughout a solid matrix and the release of the drug is controlled or sustained either by incorporating a suitable filler within the matrix or by coating the matrix with swellable or non swellable polymer film(s). Interest in oral sustained release dosage forms has brought increasing attention to multiparticulate modified release systems. Multiple-unit dosage forms are essential where drug excipients or drug-drug physicochemical interaction is possible in a single-unit formulation. They are also known to have less variance in transit time through the gastrointestinal tract than single-unit dosage forms. These dosage forms usually are based on subunits such as granules, beads, pellets, or minitablets. They are usually delivered in hard gelatin capsules or made into tablets that disintegrate instantly.

The recent interest in multiple-unit dosage forms are a result of the advantages they offer over the single unit systems. For example, multiple-unit forms offer

- More predictable gastric emptying.
- Greater statistical assurance of drug release and so more reproducible and constant drug concentration after oral administration. Therefore, inter and intra patient variability is reduced.
- Gastric emptying is less dependent on the state of nutrition.
- A high degree of dispersion in the digestive tract.
- Less absorption variability.
- Reduced risk of systemic toxicity.

- There is a greater probability of achieving total drug release from a multi particulate system than from a monolithic single – unit SR dosage form, so bioavailability can be better for multi particulate systems
- A lesser risk of dose dumping.
- Single unit system may fail to release the maintenance dose from the slow release core. This point can be critical for low solubility of drugs and/or if there is an absorption window where absorption take place in a limited region of the gastrointestinal tract.
- The multiple-unit forms are also more suitable for formulations with acid-sensitive drugs (i.e., erythromycin).

On the other hand, multiple-unit preparations exhibit some disadvantages.

- Their manufacturing is more complicated.
- More expensive.
- The filling of gelatin capsules is difficult to accomplish especially in the case where different subunits are involved.
- The preparation process of tablets necessitates extra care and fine adjustments of tabletting machines.

Although the debate on the particular advantages of two formulations (single- and multiple-unit) has been going on for a long time in the literatures. It has not produced any definite conclusion on the performance of those formulations until now and the differences in behavior are controversial.

Examples of multi particulate modified release tablets

The compaction of beads is a challenging area and only a few multiple unit containing tablet products are available such as Beloc ZOK which releases metoprolol succinate with zero order kinetics and Antra MUPS (Astra Zeneca Sodertalje, Sweden) is a multiple unit pellet system for the proton pump inhibitor omeprazole.

MICROENCAPSULATION [5]

A process in which very thin coatings of polymeric material(s) are deposited around particles of solids or droplets of liquid.

Different terms for solid particle systems are employed in drug delivery among them pellets, beads, microcapsules, microspheres, millispheres are few. The terminologies of most relevant multiparticulate systems are provided here.

Pellets can be defined as "Small, free flowing spherical particles manufactured by agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment." The size of these particles are usually between 0.5 and 1.5 mm. Sphericity and intra granular porosity are the two important quality attributes of pellets. The terms 'spherical granules' and 'beads' have been applied interchangeably to pellet system.

Microspheres are solids approximately spherical particles ranging in size from 1 to 1000 μm. They are made of polymeric, waxy, or other protective materials, that are biodegradable synthetic polymers and modified natural products such as gums, proteins, waxes etc.

Microsphere: The entrapped substance is dispersed throughout the microsphere matrix.

Microcapsule: The entrapped substance is completely surrounded by distinct capsule wall.

The similarities between microsphere and microcapsules are clear and illustrations of these particles are shown in **FIG: 2**

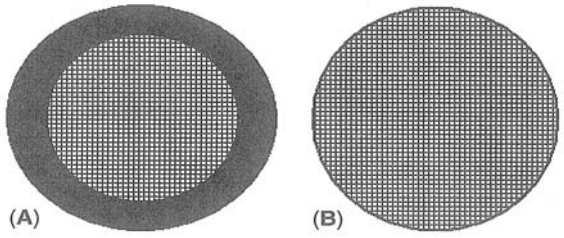


FIG: 2 (A) Microcapsule (B) Microsphere

Encapsulation methods[7]

Two major classes of encapsulation methods have evolved, viz chemical and physical. The first class of encapsulation involves polymerization during the process of preparing the microcapsules. Examples of this class are usually known by the name of interfacial polymerization or *in situ* polymerization. The second type involves controlled precipitation of a polymeric solution where in physical changes usually occur.

The precipitation and/or gelation listed in **Table: 3** cover many techniques. One example is the precipitation of water soluble polymers such as gelatin with water miscible solvents such as isopropanol. Other examples include the precipitation of ethyl cellulose from cyclohexane by cooling, and the gelation of sodium alginate with aqueous calcium salt solutions. In

all cases the objective is to precipitate a performed polymer around the core (sometimes a multi- particulate) to cause encapsulation.

Table: 3 Methods of Precipitation and/or Gelation[7]

Process	Coating material	Suspended medium
Interfacial polymerization	Water-soluble and insoluble monomers	Aqueous/organic solvents
Complex coacervation	Water-soluble polyelectrolyte	Water
Simple Coacervation	Hydrophobic polymers	Organic solvents
Thermal denaturation	Proteins	Organic solvents
Salting out	Water-soluble polymer	Water
Solvent evaporation	Hydrophilic or hydrophobic polymer	Organic or Water
Hot melt	Hydrophilic or hydrophobic polymer	Aqueous/organic solvents
Solvent removal	Hydrophilic or hydrophobic polymer	Organic solvents
Spray drying	Hydrophilic or hydrophobic polymer	Air, nitrogen
Phase separation	Hydrophilic or hydrophobic polymer	Aqueous/organic solvents

POLYMER BASED DRUG DELIVERY SYSTEM[8]:

There has been growing interest in polymer based bioadhesive drug delivery systems. One of the goals of such systems is to prolong the residence time of a drug carrier in the Gastro Intestinal Tract (GIT). The bioadhesive bond can be of a covalent, electrostatic, hydrophobic or hydrogen bond nature. Ionic polymers are reported to be more adhesive than neutral polymers, and an increased charge density will also give better adhesion suggesting that the electrostatic interactions are of great importance. Except for the oesophagus, the entire GI tract including the stomach is covered with a continuous layer of insoluble mucus gel. The mucus gel mainly consists of glycoproteins, and due to their content of ester sulphate and sialic acid groups, the mucus layer has an overall strong net negative charge. The mucus layer has been considered as a possible site for bioadhesion and drug delivery by several groups.

Natural polymers

Recently, the use of natural polymers in the design of drug delivery formulation has received much attention due to their excellent biocompatibility, biodegradability, non - toxicity, and easy in availability[9].

Polymers as carriers used in drug delivery system [10]

The different types of polymers for extended release preparations are given below:

Biodegradable Polymers:

The biodegradable polymers comprised of monomers linked to one another through functional groups and have unstable linkages in the backbone. They are biologically degraded or eroded by enzymes or generated by surrounding living cells.

- **Natural**

Albumin, Alginate, Collagen, Starch, Chitosan, Dextran, Casein, Gelatin, Fibrinogen, etc.

- **Synthetic**

Poly alkyl-cyanoacrylate, Poly ethyl-cyanoacrylate, Poly amino acids, Poly amides, Poly acryl amides, etc.

- **Aliphatic Polyesters**

Poly (malic acid), Poly (glycolic acid), Poly (hydroxyl butyrate), Poly (lactic acid), Poly Vinyl Alcohol (PVA) etc.

Non-Biodegradable Polymers :

Poly Ethylene Vinyl Acetate (EVA), Poly Ether Urethane (PEU), Cellulose Acetate, Poly Vinyl Chloride (PVC), Ethyl Cellulose,etc

In recent years a large number of biodegradable polymers have been investigated for their potential use as drug delivery systems. Among them, sodium alginate and chitosan are very promising and have been widely exploited in pharmaceutical industry for sustained drug release. Polysaccharides such as alginic acid, agar, chitin and chitosan have been used to agglomerate drugs for controlled drug delivery systems.

Chitosan is a naturally occurring polysaccharide comprising glucosamine and N-acetyl glucosamine with unique polycation characteristics. The poly cationic nature of chitosan leads to a strong interaction with negatively charged alginate. When alginate is dropped into chitosan solution, the electrostatic interaction of carboxylic groups of alginate with the amine groups of chitosan results in the formation of a membrane on the surface of sodium alginate and improves the stability and drug content[8]. This process has been widely used in the preparation of alginate–chitosan membranes with a solid calcium–alginate gel core.

There are many advantages of the chitosan coating, such as the improvement of drug loading and bioadhesive property, as well as the prolonged drug release properties etc.

Alginate (ionic, hydrophilic polymer) is a negatively charged polysaccharide with high charge density and has been reported to be bioadhesive. Among polyanionic polymers, alginate has been widely studied and applied for its possibility to modulate the release, according to the properties of its carboxyl groups as well as its biodegradability and absence of toxicity. Alginate is a naturally derived anionic polysaccharide mainly from algae belonging to the family *phaeophyceae.* Alginic acid is an algal polysaccharide and a species of polycarboxylic acid. Alginate consists of two sugar moieties β-D-mannuronic acid and α -L-guluronic acid which exists either in blocks or random sequences and their relative proportions determine the biofunctional properties of alginic acid. Alginate is known to form complexes with divalent cations, such as Ca^{2+}, Ba^{2+}, and Sr^{2+} in aqueous solution. Depending upon the composition of two sugar residues and sequential distribution within the molecules, the complexes form either precipitates or hydrogels. Guluronic acid blocks are known to form a rigid buckled structure, the so-called 'egg-box' array, in which chelating calcium ions are nestled in the aqueous environment of the ordered gel structure due to the spatial arrangements of guluronic block oxygen atoms of carboxyl and hydroxyl groups [11].

Alginate has been widely used as food additive, a tablet disintegrator or gelation agent, and the mechanism of its gelation have been extensively investigated. When an aqueous solution of sodium alginate (SA) is added drop wise to an aqueous solution of calcium chloride, spherical alginate beads with regular shape and size are produced, since an insoluble calcium alginate matrix is formed by the cation exchange between sodium and

calcium ions. Alginates are known to form reticulated structure when in contact with calcium chloride ions and this characteristic has been used to produce SR particulate systems for a variety of drugs[12].

GEL FORMATION (GENERAL MECHANISM):

A gel, in classical colloid terminology, is defined as a system which owes its characteristic properties to a cross linked network of polymeric chains which form at the gel point. A considerable amount of research has been carried out in recent years to elucidate the nature of the cross-links and determine the structure of alginate gels. Alginate beads can be prepared by extruding a solution of sodium alginate containing the desired drug or protein, as droplets, into a divalent cross linking solution such as Ca^{2+}, Sr^{2+}, or Ba^{2+}. Monovalent cations do not induce gelation while Ba^{2+} and Sr^{2+} ions produce stronger alginate gels than Ca^{2+}. Other divalent cations such as Pb^{2+},Cu^{2+},Cd^{2+},CO^{2+}, Ni^{2+}, $Zn^{2+}$and Mn^{2+} will also cross link alginate gels but their use is limited due to their toxicity. The gelation and cross linking of the polymers are mainly achieved by the exchange of divalent cations and stacking of these guluronic acids with the divalent cations, and the stacking of these guluronic groups to form the characteristic egg – box structure[13] shown in **Fig:3**

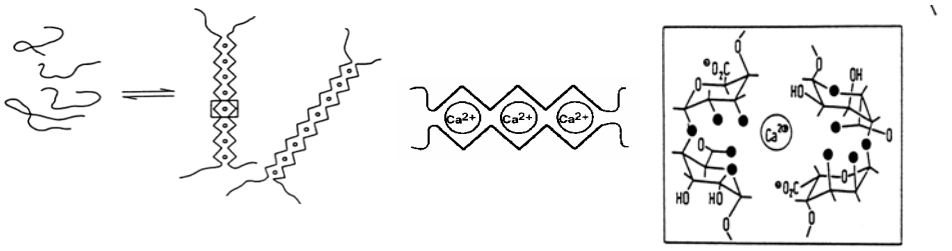


FIG: 3 Schematic representation of the egg-box association of the poly-l-L-guluronate sequences of alginate cross linked by calcium ions. The left section of the figure shows conversion of random coils to buckled ribbon like structures which contain arrays of Ca^{2+} ions. The extreme right section shows the proposed stereochemistry of Ca^{2+} ion complexation. The oxygen atoms involved in the coordination sphere are shown as filled circles.

LARGE BEAD PREPARATION

In general, beads greater are than 1.0 mm in diameter which can be produced by using a syringe with a needle or a pipette. Sodium alginate solution that contains solubilized drug or protein is transferred drop wise into a gently agitated divalent cross linking solution. The diameter of the beads formed is dependent on the size of the needle used and the viscosity of the alginate solution. A larger diameter needle and higher viscosity solutions will produce larger diameter beads. The viscosity of SA can also influence the shape of the microbeads produced. The beads become more spherical as the concentration of SA increased. However, in general SA solutions of greater than 5% are difficult to prepare.

Since gelation occurs in an aqueous environment, alginate is a promising material as a food additive, drug formulation and useful even for encapsulation of living cells to protect them from immune responses. Utilizing this stable complex formation with divalent cations, alginate gels have been utilized for investigation of cells are considered to be the ultimate system for the pulsatile release of biologically active compounds.

Formulation of delivery devices for protein and peptide drugs under aqueous conditions are desirable to avoid the undesirable decrease of bioactivities which may occur when using organic solvents and/or heat during formulations. Since relatively stable alginate gels can be formed in aqueous environments through chelation or complexation, which are more promising delivery of matrixes for bioactive compounds.

It has been suggested that the cross links were caused either by ionic bridging of two carboxyl groups on adjacent polymer chains via calcium ions or by chelation of single calcium ions by hydroxyl and carboxyl groups on each of a pair of polymer chains[7]. Although these bonds may play a role in the gelation mechanism, which are not sufficiently energetically

favorable to account for the gelation of alginate. It has been shown on the basis of fiber diffraction data and model-building calculations that the shape of both polymannuronic acid segments and the polygulutended, and that these extended ribbons can stack together in sheets. On the basis of these data and the properties of gels, it has been suggested that the cooperative association of either polymannuronic acid segments or polyguluronic acid segments are involved in the formation of the cross-linked network of polymer chain[7].

This technique has shown attractive applications in different fields, including cell immobilization, owing to its mild operative conditions. As the encapsulation method is mild, and done at room temperature in aqueous medium, several sensitive drugs, proteins, living cells, enzymes, spermatozoa etc. have been successfully encapsulated through alginate beads.

The primary structure of the alginates depends on the producing species, and for the marine species seasonal and geographical changes might result in variations in alginates extracted from the same species. The polymer is known to form a physical gel by hydrogen bonding at low pH (acid gel) and by ionic interactions with polyvalent cations such as calcium, the cation acting as a cross linker between the polymer chains. The viscosity and primary structure of the polymer are important features determining its swelling and gelling properties[14].

At neutral pH, sodium alginate is soluble and hydrates to form viscous solutions, but below pH 3, alginic acid, water swellable but insoluble, which is rapidly formed. Since the hydration characteristics of the polymer and the subsequent physical properties of the hydrated gel layer may critically influence drug release[15].

When CA beads are treated with 0.1M HCl, alginate gets hydrolyzed to lower molecular weight fractions of alginic acid. Due to conversion of COO^- group into unionized carboxylic group, the electrostatic attraction between Ca^{2+} ions and COO^- ions in the egg-box junction almost disappears. Moreover, there may occur ion-exchange between H^+ ions (presence in the external HCl solution) and free Ca^{2+} ions inside the beads. Thus a reduced Ca^{2+} ions concentration within the beads results in a weaker Ca^{2+} cross linked beads when put in phosphate buffer at pH 7.4. Therefore, the acid-treated beads are a loosely cross linked structure containing more soluble alginate as constituent. When such beads are put in the phosphate buffer of pH 7.4, the beads swell at faster rate but do not attain a higher water uptake value due to loosely bound structure of the beads which is unable to retain large amount of water within the matrix. Moreover, there is possibility of ion-exchange between H^+ ions produced due to ionization of carboxylic groups in the buffer of pH.

A group of scientist developed a method of enclosing viable cells, tissues, and other labile biological substances within a semi permeable membrane. Preliminary *in vitro* studies of several types of microencapsulated cells and tissues (red blood cells, sperm cells, hepatica cells, hepatocytes, pancreatic endocrine tissues, and islets) were described by them. Essentially, the process involves suspending the living cells or tissues in sodium alginate solution. The cell or tissue suspension is extruded through a device producing micro droplets which fall into a calcium chloride solution and form gelled microbeads with the cells or tissues entrapped. These cell-containing, gel micro beads are next treated with a solution of polysine which displaces the surface layer of calcium ions and forms a permanent polysalt shell or membrane. Finally, the interior calcium

alginate is "liquefied," either to stay in or to come out (depending on molecular weight and size of the starting alginate) of the capsule with a calcium sequestrant such as buffered citrate solution.

Gohel et al[7]., prepared diclofenac sodium microspheres by using sodium alginate as a polymer and $CaCl_2$ as a cross linking agent. In this investigation stirring speed, concentration of cross linking agent and heavy liquid paraffin were studied, on the time required for 80% drug dissolution. A statistical model with significant interaction terms was derived to predict t_{80} and the drug was released by diffusion of anomalous type. The results of multiple linear regression analysis and F value statistics revealed that, obtaining of controlled drug release and the microspheres were to be prepared using relatively lower stirring speed.

Literature reports indicate widespread use of sodium alginate for achieving sustained release of drugs, targeting gastric mucosa, and increasing the bioavailability of drugs because of sodium alginate's ability to form a stable and bioahesive gel with calcium ions[13].

Alginate also has several unique properties that have enabled it to be used as a matrix for the entrapment and/or delivery of a variety of proteins, macromolecules and cells.

HIGHLIGHTS OF ALGINATE BEADS[16]

- A relatively inert aqueous environment within the matrix.
- A mild room temperature encapsulation process free of organic solvents.
- A high gel porosity which allows for high diffusion rates of macromolecules.
- The ability to control this porosity with simple coating procedures.
- Dissolution and biodegradation of the system under normal physiological conditions.

LITERATURE REVIEW

Parul Trivedi. et al[17]., (2008) in their work **"Preparation and characterization of Aceclofenac microspheres"** reported that microspheres were prepared by o/w emulsion solvent evaporation technique using Eudragit [S 100, RL 100 and RS 100] to provide controlled release and minimizes local side effects by avoiding the drug release in the upper gastro intestinal tract. Prepared microspheres were subjected to micromeritic evaluation, drug loading studies, and *in vitro* drug release stud ies. The drug polymer concentration in the dispersed phase influence the particle size and drug release properties and all the formulations at higher pH follow the Matrix-Higuchi model.

Das MK. et al[18]., (2008) in their work **"Furosemide loaded alginate microspheres prepared by ionic cross linking technique: morphology and release characteristics"** reported that entrapment efficiency and particle size increased with the increased sodium alginate concentration. The kinetic modeling of the release data indicate that furosemide release from the alginate microspheres follow anomalous transport mechanism after an initial lag period when the drug release mechanism was found to be fickian diffusion controlled.

Srinatha A. et al[19]., (2008) in their work "**Ionic cross - linked chitosan beads for extended release of Ciprofloxacin: *In vitro* characterization**" reported that chitosan beads loaded with Ciprofloxacin HCl were prepared with ionic cross linking with sodium tripolyphosphate. High drug load was achieved within the bead with a short curing time. The release was increased with increasing concentrations of ciprofloxacin and decreasing proportion of chitosan. The drug release follows by non- fickian release mechanism.

Li Jun. et al[20]., (2007) in their work "**Preparation of procaine haemoglobin microcapsules of chitosan-sodium alginate"** reported that microcapsules were prepared by using an emulsification gelation method. Microcapsules possess a relatively narrow and normal Gaussian distribution. The procaine hemoglobin released from microcapsules were extended for more than one month.Chitosan-sodium alginate hemoglobin microcapsules were expected to become an artificial oxygen carrying therapeutic agent with SR for intravenous injection.

Shishu. et al[21]., (2007) in their work **"Stomach specific drug delivery of 5-Fluorouracil (5-FU) using floating alginate beads"** reported that a multiple –unit type oral floating dosage form (FDF) was developed to prolong gastric residence time, target stomach cancer, and increase drug bioavailability. The beads containing higher amounts of calcium carbonate demonstrated instantaneous, complete and excellent floating ability over a period of 24 hours. The optimized formulation was subjected to *in vivo* anti tumor studies and results indicate that FDF performed significantly better than the simple tablet dosage form.

Tamizharasi S. et al[22]., (2007) in their work **"Formulation, characterization and *In-vitro* release kinetics of Aceclofenac loaded poly (ε-caprolactone) microspheres"** reported that drug to carrier ratio-(1:4) showed highest drug entrapment and the drug released upto 15 hour and found to be sustained. There was no interaction between drug and polymer.

Arshia Sheriff. et al[23]., (2007) in their work "**Entrapment of Andrographolide in cross linked alginate pellets:I Formulation and evaluation of associated release kinetics"** reported that andrographolide can be converted to bitterless multiple unit dose oral delivery systems by utilizing the technique of ionotropic gelation. Several processing parameters were analyzed and finally pellets prepared by 2.5%w/v of sodium alginate into a 2%w/v solution of calcium chloride using 20 gauze flat tip needle and dried using a hot air oven at 60°C for 6 hours. Pellets with varied drug: polymer ratios were prepared and analyzed for release kinetics it was found to be best described by the korsemeyer – peppas equation. The formed pellets were completely bitterless with good entrapment efficiency and a maximum release of 86% of andrographolide preferably away from the stomach.

Thaned Pongjanyakul. et al[24]., (2007) in their work "**Xanthan alginate composite gel beads: Molecular interaction and *in vitro* characterization**" reported that composite beads consisting of Xanthan Gum (XG), Sodium Alginate (SA) and beads of Diclofenac Calcium Alginate (DCA) incorporated with different amounts of XG were prepared by using ionotropic gelation method. Molecular interaction and physical properties of composite and XG-DCA beads were evaluated. XG could form inter molecular hydrogen bonding with SA in the composite beads with or without Diclofenac Sodium (DS). Higher the content of XG in the DCA beads increased the drug entrapment efficiency and release rate of drug. It can be concluded that XG could modulate physicochemical properties and drug release of the DCA beads, which based on the existence of molecular interaction between the XG and SA.

`Shende PK. et al[25]., (2007) in their work **"Formulation and characterization of alginate-gelatin beads for controlled release of Glipizide"** reported that modification in matrix structure of alginate could be done by addition of gelatin and the alginate-gelatin matrix does not interfere with glipizide. Glipizide seems not to be involved in the cross linking reaction, which appears to occur only between gelatin, alginate and formaldehyde which were used as cross-linking agent.

Manjunatha KM. et.al[26]., (2007) in their work **"Design and Evaluation of Diclofenac sodium controlled drug delivery system"** reported that the immediate release component and controlled release component were prepared by using mannitol and sodium alginate respectively. Poly vinyl pyrolidine and mannitol were used as carriers for drug in preparing solid dispersion and this solid dispersion form shown increased the solubility of the drug. The prepared controlled release beads were sufficiently hard and sustained the release of drug for long duration.

Sahoo SK. et al[27]., (2007) in their work **"Formulation and *in vitro* evaluation of alginate beads of Aceclofenac by ionotropic gelation technique"** reported that the drug loaded beads showed 70 to 80 % of drug entrapment, which was found to increase with increase in sodium alginate concentration. The release of aceclofenac was found to be affected both by concentration of polymer and cross linking agent (calcium chloride).

Raida S Al-kassas. et al[28]., (2007) in their work "**Controlling of systemic absorption of Gliclazide through incorporation into alginate beads**" reported that alginates have the advantages of swelling and mucoadhesive properties, so that it could be used to improve the oral delivery of the antidiabetic agent gliclazide. The swelling behavior of the beads strongly dependent on the polymer concentration in the formulation and pH of the medium.

Thaned pongjanyakul. et al[29]., (2006) in their work **"Modulation of drug release from glyceryl palmitostearate-alginate beads via heat treatment"** reported that incorporation of glyceryl palmitostearate (GPS) into the diclofenac calcium alginate (DCA) beads increased particle size and entrapment efficiency of diclofenac sodium (DS), but decreased water uptake in distilled water and DS release rate. The heat treatment caused the DCA beads to be irregular shape particles and to possess higher water uptake. A slower release rate of DS in distilled water was found because of interaction of DS and alginate polymer matrix, a restriction of water sorption into the inside region of the beads, which caused by the shrinkage after heating.

Sameer sharma. et al[30]., (2006) in their work "**Low density multiparticulate system for pulsatile release of Meloxicam"** reported that floating pulsatile drug delivery system was developed using porous calcium silicate (Florite RE) and sodium alginate, for time and site specific drug release of meloxicam. Drug adsorbed Florite RE powder was used to prepare calcium alginate beads by ionotropic gelation method, using 3^2 factorial designs and evaluated. The floating time was controlled by density

of beads and hydrophobic character of drug. A pulsatile release of meloxicam was demonstrated by a simple drug delivery system which could be useful in chronopharmaco therapy of rheumatoid arthritis.

Yagnesh L.Patel. et al[31] ., (2006) in their work "**The effect of drug concentration and curing time on processing and properties of calcium alginate beads containing metronidazole by response surface methodology**" reported that preparation of calcium alginate beads containing metronidazole using 3^2 factorial design, with drug concentration and curing time as variables. Entrapment efficiency decreased with decrease in polymer concentration and increasing in curing time. In acidic medium, the swelling and drug release properties were influenced by drug solubility, where as in basic medium these properties were governed by the gelling of polymer and exhibited curvilinear and quadratic functions of both the variables respectively.

Satit Puttipipatkhachorn. et al[32]., (2005) in their work **"Molecular interaction in alginate beads reinforced with sodium starch glycolate or magnesium aluminum silicate and their physical characteristics"** reported that the additives Sodium Starch Glycolate (SSG) or Magnesium Aluminum Silicate (MAS) could improve the entrapment efficiency of Diclofenac Calcium Alginate (DCA) beads. The swelling and water uptake of the beads depend on the properties of incorporated additives. The SSG-DCA beads showed a higher water uptake and swelling than MAS-DCA beads. The release kinetic of the beads in pH 6.8 phosphate buffer was swelling controlled mechanism, while that in distilled water followed Higuchi's model.

Gohel MC. et al[33]., (2005) in their work **"Preparation and formulation optimization of sugar crosslinked gelatin microspheres of Diclofenac Sodium"** reported that sugar (e.g glucose, fructose) can induce cross linking of gelation for the preparation of modified release microspheres. The microspheres which were prepared by emulsion crosslinking method revealed that, the parameters such as drug to gelatin ratio, volume of light liquid paraffin and stirring rate were found to affect the morphology and drug release of microspheres.

Anil.K.Anal. et al[34]., (2005) in their work "**Chitosan alginate multilayer beads for controlled release of Ampicillin**" reported that ionotropic gelation was used to prepare single and multi layer beads of ampicillin using various combinations of chitosan and Ca^{2+} as cationic components and alginate, polyphosphate as anions. Beads prepared with higher concentrations of chitosan entrapped more ampicillin. Single and multilayer chitosan alginate beads release faster than polyphosphate cross linked multi layer beads and it offers an opportunity for controlled gastrointestinal passage of compounds with low molecular weight like ampicillin.

Dandagi PM. et al[35]., (2004) in their work "**Microencapsulation of Verapamil Hydrochloride by Ionotropic gelation technique"** reported that, increased in speed of rotation of calcium chloride (counter-ion) solution, leads to decreased in pellet size. Also it was found that with the increase in harvesting time, the pellet formed in turn decreased the drug entrapment efficiency. The release of the drug from micro pellets was found to be following non-fickian diffusion mechanism, which accounts for the prolonged release of verapamil hydrochloride.

Mishara. et al[36]., (2003) in their work **"Development of chitosan – alginate microcapsules for colon specific delivery of Metronidazole"** reported that microcapsules prepared by calcium chloride cross linking method with different concentration of sodium alginate and chitosan. Then they were treated for three different coating with reduced molecular weight chitosan, guar gum and enteric coatings with cellulose acetate pthalate. Chitosan concentration significantly affected the strength and flexibility of membrane. Drug loading was decreased with increase in the weight of either encapsulating polymer or chitosan and different coatings. *In vitro* drug release was found to be decreased with increasing chitosan and sodium alginate concentrations. Among the three coatings reduced molecular weight chitosan coating gave much lower drug release and exhibit colon specificity.

Gonzalez-Rodriguez ML. et al[37]., (2002) in their work "**Alginate /chitosan particulate systems for sodium Diclofenac Release**" reported that microspheres were prepared by ionic gelation (Ca^{2+} and Al^{3+}) and characterized by electron microscopy and differential scanning calorimetry. The release of diclofenac sodium was prevented at acidic pH, while it was complete in a few minutes when pH is raised up to 6.4 and 7.2.The alginate / chitosan ratio and nature of gelifying cation allow a control of the release rate of the drug.

Bhupender Singh. et al[38]., (2002) in their work **"Design, development and optimization of controlled release microcapsules of Diltiazem Hydrochloride"** reported that microcapsules were formulated as per factorial design taking rate controlling coat polymer and emulgent that is ethylcellulose and span 80 respectively. The release of drug follows fickian drug release. The release was found to be quite regulated for controlled release purpose ($t_{80\%}$ ≈9.5hr) with little dose dumping (release upto 16hr≈99%).

Shymala Baskaran. et al[39]., (2000) in their work **"Preparation and evaluation of alginate – chitosan beads"** reported that chitosan reacts with sodium alginate in the presence of tripolyphosphate for beads formation. diltiazem HCl was used as the model drug. Spherical beads were produced with diameter in the range of 400-600µm.The encapsulation efficiency was found to be 80-90% and there was a rapid initial drug release phase followed by a second release phase, but when glutaraldehyde or pectin is added the burst effect disappeared and they also decreased the percentage release of drug from the beads.

Lin sy. et al[40]., (1992) in their work **"Calcium alginate beads as core carriers of 5–Amino Salicylic Acid"** reported that the utilization of calcium alginate beads as core carriers for delayed dissolution followed by burst release as a potential method of intestinal site specific drug delivery was investigated. 5–amino salicylic acid was spray coated on dried calcium alginate beads and then coated with different percentages of enteric coating polymer and /or sustained release polymer. This dosage form provides the possibility to deliver drug to the lower intestinal tract with minimal early release followed by sustained release in the colon.

Chowdary KPR. et al[41]., (1989) in their work "**Studies on microencapsulation by calcium alginate"** reported that method based on emulsification of a solution of sodium alginate containing the drug in an immiscible liquid medium followed by curing with calcium chloride to result in spherical calcium alginate microcapsules were reported. Aspirin, diazepam and nitrofurantoin were encapsulated by this method. The microcapsules were found to release the drug slow and spread over extended period of time. The release mechanism was found to be of diffusion type.

SCOPE OF THE WORK

Treatment for an ailment by the physician mostly involved drug substances. The use of drug substances had become inevitable in the modern days. The major problems faced by patients in taking the medications are to be overcome by altering the design of dosage form or properties of the drug moiety.

The scope of any formulation primarily focuses on safety and efficacy of the drug delivery system. Now the focus has been slightly moved to the patient's convenience and acceptance. Where still the safety and efficacy remain integrated with design.

Recent research efforts through out the world have resulted in significant development of novel drug delivery systems. Among the systems one of the common methods of controlling the rate of drug release is microencapsulation and resulting beads have gained good acceptance as a process to achieve the sustained release.

There has been growing interest in the use of natural polymers as a drug carrier due to their biocompatibility, biodegradability, non-toxicity and easy in availability. Alginates, which are naturally occurring polysaccharides obtained from marine brown algae have received much attention ass a vehicle for sustained drug delivery.

The formation of calcium alginate beads by ionotropic gelation was achieved by dropping the drug containing sodium alginate dispersion into calcium chloride bath. Calcium induced alginate gel beads have developed in recent years as a unique vehicle for drug delivery systems.

ALGINATE BEADS HAVE THE FOLLOWING ADVANTAGES [42]

- Alginate is known to be nontoxic as taken orally and to protect the mucous membrane of the upper gastrointestinal tract from the irritation of chemicals.
- Since dried alginate beads have the property of reswelling, they can act as a sustained -release system.
- Since the property of reswelling is susceptible to the environmental pH, acid-sensitive drugs incorporated into the beads would be protected from gastric juice.

Therefore, drug-loaded alginate beads might provide these advantages for non - steroidal anti-inflammatory drugs (NSAIDs) such as aceclofenac used extensively in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Aceclofenac is one of the emerging NSAID molecules and having short biological half – life 4 hours, minimizes local side effects by avoiding the drug release in the upper gastro intestinal tract dosing frequency is more than one time which makes it more potential candidate for developing for sustained release.

Much attention has received the chitosan–alginate polyelectrolyte complex that has been studied thoroughly. Chitosan is used either as a means of coating alginate beads in order to alter the diffusion rate of the encapsulated substances. The behavior of calcium–alginate beads treated with chitosan in media that imitate the gastrointestinal fluids has been studied by several researchers.

OBJECTIVE

The use of natural polymers as drug carriers is one of the main objectives of recent researchers dealing with long acting dosage forms. Among them sodium alginate has been widely studied and applied for its possibility to modulate the release, according to its properties of its carboxyl groups by addition of multivalent ions as well as its biodegradability and absence of toxicity.

Aceclofenac is NSAID used extensively in the rheumatoid arthritis, osteoarthritis and having short biological half life of 4 hours, minimizes local side effects by avoiding the drug release in the upper gastro intestinal tract and dosing frequency more than one time make it an ideal candidate for sustained release multi particulate drug delivery system.

In this present study alginate beads containing aceclofenac were prepared by using sodium alginate a natural, hydrophilic polymer and calcium chloride as cross – linking agent. The influence of

- The concentration of sodium alginate
- Concentration of cross linking agent
- Different curing time intervals
- Different cross linking agents and
- Addition of chitosan to calcium chloride were studied with,

IR and DSC for Drug interactions studies, Physical characterization of the formulations by optical microscope, Scanning Electron Microscope, and X-Ray Diffractrometry to characterize the bead. The formulations were further analysed for encapsulation efficiency, *in vitro* drug release and kinetics studies.

PLAN OF THE WORK

The work entitled, **"FORMULATION, PHYSICAL CHARACTERIZATION AND *IN VITRO* RELEASE STUDIES OF ACECLOFENAC ALGINATE BEADS PREPARED BY IONOTROPIC GELATION FOR SUSTAINED RELEASE"** was planned an following in an aim to achieve the objective described earlier. The work was carried out for a period of **9 months** (May 2008 to January 2009) which was divided into three phases like

Phase I (May - June 2008)

1. Literature survey.
2. Identification of the objective for the current study.
3. Optimization of the parameters.

Phase II (July - December 2008)

1. Preparation of standard graph for the drug.
2. Preparation of alginate beads by ionotropic gelation method.
3. Evaluation of the Physical Characteristics.
   - 3.1 Compatibility study using Infra Red (IR) spectroscopy and Differential Scanning Calorimeter (DSC).
   - 3.2 Size and size distribution analysis by using an Optical Microscope.
   - 3.3 Surface morphology by using Scanning Electron Microscope (SEM).
   - 3.4 Analysis of samples by using X – Ray Diffractometer (XRD).

4. Drug content and release studies
    - 4.1 Drug entrapment efficiency.
    - 4.2 *In vitro* drug release analysis.

5. Kinetics of drug release from the formulations using
    - 5.1 Zero order release.
    - 5.2 First order release.
    - 5.3 Higuchi's model.
    - 5.4 Korsmeyer's model.

Phase III (January 2009)

1. Compilation and preparation of reports.

MATERIALS

Name of the materials	Name of the company
Aceclofenac (gift sample)	Anglo French drug industries Ltd, Bangalore
Sodium alginate AR	Hi media biosciences Ltd, Mumbai.
Calcium chloride AR	S.D.Fine chemicals Ltd, Mumbai
Aluminium Sulphate AR	Hi media Laboratories, Mumbai
Barium chloride AR	Qualigens Fine chemicals Ltd, Mumbai
Chitosan AR	Fluca Biochemica. Ltd, Switzerland. (Viscosity 200-400 mPa.s)
Methanol AR	S.D.Fine chemicals Ltd, Mumbai

EQUIPMENTS USED

Name of equipment	Name of the company
UV / Vis Spectrophotometer	JASCO V-530.
IR Spectrophotometer	Jasco-FT-IR 8201 PC
Differential scanning calorimeter	DSC-60 (Shimadzu, Tokyo, Japan)
Optical Microscope and stage Micrometer	Erma. Japan
Scanning Electron Microscope	JSM 6400
X-ray diffractrometer	Bruker AXS D8
Dissolution apparatus	Electrolab TDT-08L, USP XXIV Type I apparatus. Chennai.
Remi Hi-speed motor	Universal motors. Mumbai
Digital balance	Denver instruments
pH tester 1 (water proof)	Oakton instruments.

DRUG PROFILE

ACECLOFENAC [43-45]

Aceclofenac is from the class of Non Steroidal Anti Inflammatory Drug (NSAID). It is a derivative of aryl acetic acid.

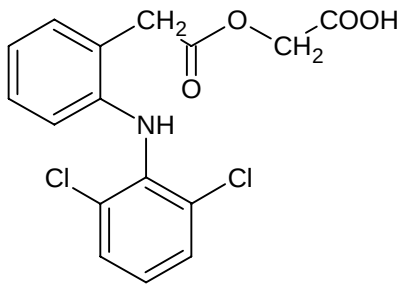
Chemical name

[[[2-[(2, 6-Dichlorophenyl) amino] phenyl] acetyl] oxy] acetic acid.

Empirical formula

$C_{16}H_{13}Cl_2NO_4$

Chemical Structure



Physical Characteristics

Colour: white.

Appearance: white, crystalline powder.

Solubility

It is practically insoluble in water, freely soluble in acetone, soluble in alcohol.

Melting point : 149°-160°C.

Molecular weight : 354.2

Half life : 4 hours.

Dose and Administration

The usual dose of aceclofenac is 100mg given orally twice daily. One tablet in the morning and the other in the evening. There is some evidence that the dose of aceclofenac should be reduced in patients with hepatic impairment and it is suggested that an initial daily dose of 100mg be used.

Over dosage

There are no human data available on the consequences of aceclofenac over dosage. The symptoms could be nausea, vomiting, stomach pain, dizziness, somnolence, and headache

PHARMACOKINETICS

Absorption

Aceclofenac is absorbed rapidly and completely after oral administration. Peak plasma concentrations are reached approximately 1-3 hours after an oral dose. The presence of food does not alter the extent of absorption of aceclofenac but the absorption rate is reduced.

Distribution

Aceclofenac is highly protein bound (~99.7%). The plasma concentration of aceclofenac was approximately twice that in synovial fluid and multiple doses of drug in patients with knee pain and synovial fluid effusion. The volume of distribution is approximately 30L.

Metabolism

Aceclofenac is metabolized into a major metabolite, 4'- hydroxyl aceclofenac and to a number of other metabolites including 5-hydroxy aceclofenac, 4'- hydroxyl diclofenac, and 5- hydroxyl diclofenac. These other metabolites account for the fate of approximately 20% of each dose of aceclofenac.

Excretion

Renal excretion is the main route of elimination of aceclofenac with 70-80% of the administered dose found in the urine, mainly as the glucuronides of aceclofenac and its metabolites. Of each of dose of aceclofenac, 20% is excreted in the faeces. The plasma elimination half-life of the drug is approximately 4 hours

Pharmacology

The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis.Aceclofenac is a potent inhibitor of the enzyme Cyclooxygenase (COX), which is involved in the production of prostaglandins. Aceclofenac has shown to exert effect on a variety of mediators of inflammation. The drug inhibits the synthesis of inflammatory cytokines interleukin (IL)-1β and inhibits Prostaglandin E_2 (PGE_2) production. *In vitro* data indicate inhibition of COX 1&2 by aceclofenac in whole blood assays; with selectively COX 2 is evident.

In contrast to some other NSAID's aceclofenac has shown stimulatory effect on cartilage matrix synthesis that may be linked to the ability of the drug to inhibit (IL) - 1β activity. There is also evidence that aceclofenac stimulates the synthesis of IL-1 receptor antagonist in human

articular chondrocytes subjected to inflammatory stimuli and that 4'-hydroxyl aceclofenac has chondro protective properties attributable to suppression of (IL) - 1β mediated promatrix metallo proteinase production and proteoglycan release.

In patients with osteoarthritis of the knee, aceclofenac decreases pain, reduces diseased severity and improves the functional capacity of the knee. It reduced joint inflammation, pain intensity and the duration of morning stiffness in patients with rheumatoid arthritis. The duration of morning stiffness and pain intensity are reduced and spinal motility improved, by aceclofenac in patients with ankylosing spondylitis.

Indications

Aceclofenac is indicated for the relief of pain and inflammation associated with rheumatoid arthritis, osteoarthritis and in ankylosing spondylitis.

Contraindications

Aceclofenac should not be administered to patients hypersensitive to aceclofenac or other NSAID's, or patients with history of aspirin or NSAID's related allergic and to patients with anaphylactic reactions or with peptic ulcers or GI bleeding, moderate of severe renal impairment.

Drug interactions

Drug interactions associated with aceclofenac are similar to those observed with other NSAID's. Aceclofenac may increase plasma concentrations of lithium, digoxin and methotrexate, increase the activity of anti coagulants, inhibit activity of diuretics, enhance cyclosporine

nephrotoxicity and precipitate convulsions when co administered with quinolone antibiotics. The co administration of aceclofenac with other NSAID's or corticosteroids may result in increased frequency of adverse events.

Adverse drug reactions

Aceclofenac is well tolerated with most adverse events being minor and reversible and affecting mainly the GI system. Most common events includes dyspepsia, and abdominal pain, dizziness, vertigo, pruritus, rash and dermatitis have been reported with aceclofenac, but the incidence of these events is less than 5%. Increases blood urea nitrogen and a blood creatinine level have been reported with aceclofenac treatment. As with other NSAID's, aceclofenac can elevate circulating levels of hepatic enzymes.

POLYMER PROFILE

SODIUM ALGINATE[46]

Alginate is linear, naturally occurring polysaccharide, consisted of β-D-mannuronic acid and α-L-guluronic acid. The ability of alginate to form gel in the presence of multivalent ions has been utilized and the material to be encapsulated is added drop wise into the multivalent ion solution. The contact of droplets with multivalent ions results in instantaneous formation of gel spheres containing uniformly dispersed material throughout the cross linked alginate matrix.

Non Proprietary Names

BP	-	Sodium alginate
Ph.Eur	-	Natrii aligns
USPNF	-	Sodium alginate

Synonyms

Algin; alginic acid, sodium salt; *kelcosol; keltone; protanal*; sodium polymannuronate.

Method of manufacturing

Alginic acid is extracted from brown seaweed and is neutralized with sodium bicarbonate to form sodium alginate.

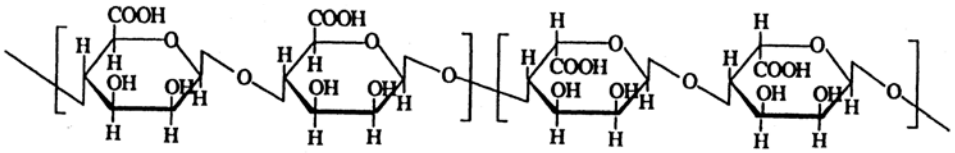
Chemical name

The chemical compound sodium alginate is the sodium salt of alginic acid.

Empirical Formula

$NaC_6H_7O_6$

Structural formula [13]



D-Mannuronic acid residues L-Guluronic acid residues

Description

Sodium alginate occurs as an odorless, tasteless, and white to pale yellowish brown colored powder.

pH

Approximately 7.2 for a 1%w/v aqueous solution.

Solubility

Practically insoluble in ethanol, ether, and chloroform. Also, practically insoluble in other organic solvents and aqueous acidic solutions in which the pH is less than 3, but it is slowly soluble in water to form a viscous colloidal solution.

Viscosity (dynamic)

Various grades of sodium alginates are commercially available that yield aqueous solutions of varying viscosity**.** Typically, a 1%w/v aqueous solution at 20°C will have a viscosity of 20-400 mPas (20- 400cp).Viscosity may vary depending upon concentration, pH, temperature, or the presence of metal ions and in general above pH 10, viscosity decreases.

Functional category

It is used as a stabilizing agent; suspending agent; tablet, capsule disintegrant; binder, viscosity modifier.

Stability and storage conditions

Sodium alginate is a hygroscopic material, although, stable at low humidities and at cool temperatures. Aqueous solutions of sodium alginate are most stable at pH 4-10. Below pH 3, alginic acid is precipitated. Sodium alginate solutions are susceptible to microbial spoilage during storage, which may affect solution viscosity. Solutions are ideally sterilized using ethylene oxide, although filtration by using a 0.45μm filter has only a slight adverse effect on solution viscosity. Subsequent loss of viscosity due to depolarization was observed when sodium alginate was heated above 70°C. Preparations containing sodium alginate, for external use may be preserved by the addition of 0.1% chlorocresol, chloroxylenol, or parabens and if the medium is acidic, benzoic acid may be used. Bulk material should be stored in an airtight container in a cool and dry place.

Incompatibilities

Sodium alginate is incompatible with acridine derivatives, crystal violet, phenyl mercuric acetate and nitrate, heavy metals and ethanol in concentrations greater than 5% w/v. Low concentrations of electrolytes cause an increase in viscosity but high electrolyte concentrations causing salting out of sodium alginate; salting out occurs if more than 4% of sodium chloride is present.

Application in pharmaceutical formulations

Sodium alginate is used in variety of oral and pharmaceutical formulations. In tablet formulations, sodium alginate may be used as both a binder and disintegrant; it has also been used as an diluents in capsule formulations and also been used in the preparation of sustained release oral formulations, since it can delay the dissolution of a drug from tablets, capsules, and aqueous suspensions.

Recently, sodium alginate has been used for the aqueous microencapsulation of drugs, in contrast with the more conventional microencapsulation techniques which use organic solvent systems. It has also been used in the formation of nanoparticles.

The adhesiveness of hydrogels prepared from sodium alginate has been investigated and the drug release from oral mucosal adhesive tablets based in sodium alginate has been reported. Hydrogel systems containing alginates have also been investigated for delivery of proteins and peptides.

Therapeutically, sodium alginate has been used in the combination with an H_2 receptor antagonist in the management of gastroesophageal reflux and as a hemostatic agent in surgical dressings. Alginate dressings, used to treat exuding wounds often contain significant amounts of sodium alginate as this improves the gelling properties. Sodium alginate is also used in cosmetics and food products at concentrations given in **Table 4.**

TABLE: 4 General uses of sodium alginate

Use	Concentration (%)
Pastes and creams	5 - 10
Stabilizer in Emulsions	1 – 3
Suspending agent	1 – 5
Tablet binder	1 – 3
Tablet disintegrant	2.5 - 10

Safety

Sodium alginate is widely used in cosmetics, food products, and pharmaceutical formulations, such as topical products, including wound dressings. It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful. The WHO has not specified an acceptable daily intake for alginic acid and alginate salts as the levels used in foods do not represent a hazard to health.

Handling precautions

Sodium alginate may be irritant to eye or respiratory system if inhaled as dust; Eye protection, gloves, dust respirator are needed while handling. Sodium alginate should be handled in a well ventilated environment.

Related substances

Alginic acid; calcium alginate; potassium alginate; propylene glycol alginate.

Calcium alginate

Synonyms

Alginic acid, calcium salt, calcium polymannuronate, calginate.

Comments

Calcium alginate is used similarly as sodium alginate in the preparation of sustained release formulations, preparations of beads, hydrogels and hemostatic wound dressings which can be washed off with sterile sodium chloride solution. The microencapsulation of live attenuated Bacillus Calmette Guerin (BCG) cells with in a calcium alginate matrix has also been reported.

CHITOSAN [47]

Chitosan is a derivative of chitin and it is a unique polysaccharide and a hydrophilic polymer.

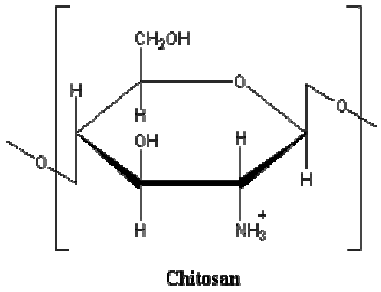
Non Proprietary Names

BP: Chitosan hydrochloride

Ph Eur: Chitosan hydrochloridum

Chemistry

Structural formula



Chitosan

Chemical Name: poly- β-(1, 4) - 2- Amino- 2-deoxy-D-glucose

Preparation

The principle derivative of chitin, namely Chitosan $(C_6H_{11}O_4N)_n$ is a unique polysaccharide and hydrophilic polymer which is taken from the chitin, a polysaccharide found in the exoskeletons of crustaceans. It is processed by removing the shells from shellfish such as shrimp, lobusters, and crabs. The shells are then ground into a pulverous powder. This powder is then deacelytated. This involves boiling Chitin in concentrated alkali (50%) for several hours. This will yield Chitosan with a degree of acetylation between 20-30%, the most popular commercial form of Chitosan. In such a Chitosan, the acetyl groups are uniformly distributed

along the polymer chain. This is in contrast with the Chitosan of similar degree of acetylation, but isolated from fungal cell walls in which the acetyl residues are grouped into clusters. Special chemical treatment is needed to obtain completely de-acetylated forms of Chitosan.

Chitin

Chitosan, partly acetylated (obtained by chemical methods)

Chitosan, partly acetylated (isolated from fungal cell wall)

Chitosan, completely de-acetylated (obtained by chemical methods)

Functional category

It is used as a **c**oating agent; disintegrant; film-forming agent; mucoadhesive; tablet binder; viscosity-increasing agent,etc.

Chemical Character

Chitosan is a cationic polyamine with a high charge density at pH < 6.5 so adheres to negatively charged surface and chelates metal ions. It is a linear polyelectrolyte with reactive hydroxyl and amino groups so available for chemical reaction and salt formation. Chitosan is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit; D) and N-acetyle-D-glucosamine (acetyle unit; A). The percentage degree of deacetylation (%DA) of Chitin can be determined by NMR spectroscopy, and the %DA in commercial Chitosan is in the range 60-100 %. The viscosity of a Chitosan solution primarily depend on the

average molecular weight of the polymer, which can be determined by size exclusion chromatography combined with light scattering detection.

The amino group in Chitosan has a pKa value of ≈6.5, thus chitosan is positively charged and soluble in acidic to neutral solution with a charge density depend on pH and the %DA. Numerous studies have demonstrated that the salt form, molecular weight, and degree of deacetylation as well as pH at which the chitosan is used all influence how this polymer is utilized in pharmaceutical application. Chitosan is incompatible with strong oxidizing agent.

Typical properties

Chitosan is a cationic polyamine with a high charge density at pH<6.5. It is linear poly electrolyte with reactive hydroxyl and amino groups. The properties of chitosan relate to its poly electrolyte and polymeric carbohydrate character. The presence of a number of amino groups allows chitosan to react chemically with anionic systems, which results in alteration of physicochemical characteristics of such combinations.

Acidity/alkalinity	pH=4 – 6 (1%w/v aqueous solution)
Density	1.35 – 1.49 g/cm^3
Particle size distribution	< 30 μm

Stability and Storage condition

Chitosan is a stable material at room temperature although it is hygroscopic after drying. Chitosan should be stored in a tightly closed container in a cool and dry place.

Incompatibilities

Chitosan is incompatible with strong oxidizing agents.

Safety

Chitosan is being investigated widely for use as an excipient in oral and other pharmaceutical formulations. It is also used in cosmetics. Chitosan is generally regarded as biodegradable, nontoxic and nonirritant material. It is biocompatible with both healthy and infected skin.

Applications

- Used in sustained drug delivery application.
- Used as a components of mucoadhesive dosage forms, rapid release dosage forms, improved peptide delivery, colonic drug delivery systems, and use for gene delivery.
- It is processed into several pharmaceutical forms including gels, films, beads, microspheres tablets and coating for liposomes.

FORMULATION OF SODIUM ALGINATE BEADS CONTAINING ACECLOFENAC[27& 34]

The beads of aceclofenac were prepared by ionotropic gelation technique as described in Sahoo S.K. et al. 100ml of Sodium Alginate (SA) solution at different concentrations were prepared by stirring sodium alginate powder in deionized water for 30 minutes then, an accurately weighed quantity of aceclofenac was added to afford homogenous dispersions. The SA-drug dispersion were then added drop wise into a 100ml of cross linking solution (different concentration and type) using a 10ml of hypodermic syringe fitted with a 20 gauge needle and stirred at 500 rpm. The formed alginate beads were cured at different time intervals. On expiration of this period the solution of cross linking agent was decanted and the alginate beads were washed repetitively for three times with 50ml deionized water. The alginate beads were thereafter dried at 60°C for 2 hours in a hot air oven. Similarly, chitosan – alginate beads were also prepared with a defined amount of chitosan, previously dissolved in acetic acid solution which was then added in the cross linking solution. The variables chosen in the present work includes concentration of sodium alginate, concentration of cross-linking agent, different curing time intervals, different cross linking agents, and addition of chitosan were studied. The details of the formulations prepared were given in the **Table 5.**

TABLE: 5 COMPOSITIONS OF DIFFERENT BATCHES OF ALGINATE BEADS PREPARED

Formulation code	Drug (mg)	Sodium alginate (%w/v)	Cross-linking type	Cross-linking (%w/v)	Curing time (min)
F1	200	2.5	$CaCl_2$	3	30
F2	200	2.5	$CaCl_2$	3	30
F3	200	2.5	$CaCl_2$	3	30
F4	200	2.5	$CaCl_2$	3	30
F5	200	2.5	$CaCl_2$	3	30
F6	200	2.5	$CaCl_2$	1	30
F7	200	2.5	$CaCl_2$	2	30
F8	200	2.5	$CaCl_2$	4	30
F9	200	2.5	$CaCl_2$	5	30
F10	200	2.5	$CaCl_2$	3	15
F11	200	2.5	$CaCl_2$	3	60
F12	200	2.5	$CaCl_2$	3	120
F13	200	2.5	$CaCl_2$	3	240
F14	200	2.5	$BaCl_2$	3	30
F15	200	2.5	$Al_2(SO_4)_3$	3	30
F16	200	2.5	Chitosan+ $CaCl_2$	1.5 +1.5	30

COMPATIBILITY STUDIES

One of the requirements for the selection of suitable polymers or carriers for pharmaceutical formulation is its compatibility. Therefore in the present work a compatibility study was done by using Infra Red spectroscopy (IR) and Differential Scanning Calorimetry (DSC) to find out if there is any possible chemical interaction between aceclofenac and the polymers.

IR SPECTRAL ANALYSIS

Weighed amount of the drug was mixed thoroughly with 100mg of potassium bromide (dried at 40° - 50° C) and compressed under 10 ton pressure in a hydraulic press to form a pellet which was then scanned from 4000 - 400^{-1}cm using FTIR 8201 PC spectrophotometer. The same procedure was repeated for polymers and other formulations prepared. The IR spectrum of aceclofenac and polymer was compared with IR spectrum of prepared formulation.

DIFFERENTIAL SCANNING CALORIMETRY (DSC) [48]

Differential Scanning Calorimetry analysis was used to characterize the thermal behavior of the drug substances. It was performed by using DSC-60 (Shimadzu, Tokyo, Japan) calorimeter to study the thermal behavior of selected formulations. The instrument comprised of calorimeter (DSC 60), flow controller (FCL60), thermal analyzer (TA 60) and operating software (TA 60). The samples were heated in hermetically sealed aluminum pans under nitrogen flow (30 ml/min) at a scanning rate of 5ºC/min from 24±1ºC to 300ºC. An empty aluminum pan, sealed in the same way as the sample, was used as a reference.

PHYSICAL CHARACTERIZATION

DETERMINATION OF PARTICLE SIZE AND SIZE DISTRIBUTION ANALYSIS

The particle size and distribution analysis were determined using an optical microscope. In this method a slide containing alginate beads were taken and 100 beads were subjected for particle size analysis using a calibrated optical micrometer. Each formulation were then evaluated in triplicate.

Standardization of eye piece micrometer[49]

Calibrate the eyepiece micrometer with the help of the stage micrometer (standard). Note the division of the eye piece micrometer scale and stage micrometer scale which coincide with each other, use the following formula to asses how much is one division of eye piece micrometer.

One division of stage micrometer = 10μ

$$1\,\text{division of eyepiece micrometer} = \frac{\text{Number of division of stage micrometer X 10}}{\text{Number of division of eyepiece micrometer}}$$

After obtaining the required data like frequency of particle in each size range (number distribution), the statistical diameters were calculated using the following Edmundson equation. The **Table 6** given below explains how the statistical diameters were calculated.

$$\text{d mean} = \left(\frac{\sum \text{nd}^{\text{p+f}}}{\sum \text{nd}^{\text{f}}} \right)^{1/p}$$

n = number of particles in a size range in μm

d = mid point in a size range

p = an index related to size of an individual particle represents.

If p =1, 2, 3 represents length, surface, volume respectively

p = positive –arithmetic mean

p = negative –harmonic mean

p = zero – geometric mean

f = 0,1,2,3

Table: 6 Statistical diameters

$\left(\frac{\sum \text{nd}^{\text{p+f}}}{\sum \text{nd}^{\text{f}}} \right)^{1/}$	**P**	**f**	**Type of mean**	**Size parameter**	**Frequency**	**Mean Diameter**
$\left(\frac{\sum \text{nd}}{\sum \text{n}} \right)$	1	0	Arithmetic	Length	Number	Length – number mean d_{in}
$\sqrt{\frac{\sum nd^2}{\sum n}}$	2	0	Arithmetic	Surface	Number	Surface – number mean d_{sn}
$\sqrt[3]{\frac{\sum nd^3}{\sum n}}$	3	0	Arithmetic	Volume	Number	Volume– number mean d_{vn}
$\frac{\sum nd^3}{\sum nd^2}$	1	2	Arithmetic	Length	Surface	Volume – Surface or surface – weighted mean, d_{vs}

SCANNING ELECTRON MICROSCOPY

The purpose of the Scanning Electron Microscope (SEM) study was to obtain the surface topographical characterization of the beads. SEM photographs of prepared formulations were taken with (Instrument JSM-6390) at different magnification ranging from 30 to 5000X at room temperature. The samples were mounted on double-sided adhesive tape that has previously been secured on copper stubs. The acceleration voltage was maintained at 20kv, with a Secondary Electron Image (SEI) as a detector.

X-RAY DIFFRACTROMETRY [27] (X-RD)

The X-ray diffraction patterns of pure drug and the selected formulation were recorded using a X-ray diffractrometry which was carried out to investigate the effect of microencapsulation process on crystallinility of drug. The X-RD patterns of drug powder and drug loaded beads were recorded using Bruker AXS D8 Advance X-ray diffractometer with a copper target. The conditions were: voltage -30 kV, current -30 mA, scanning speed -1/min. Temperature of acquisition: room temperature; Detector: scintillation counter detector.

DRUG CONTENT ANALYSIS

DETERMINATION OF DRUG ENTRAPMENT EFFICIENCY[17]

Fifty milligrams of drug loaded alginate beads from each batch was placed in 100 ml conical flask containing 50 ml of phosphate buffer (pH 7.4). The beads were agitated on mechanical shaker for 24 hours, to promote swelling and break up of the cross - linked structure. Then solutions were filtered and the drug was quantified at 274 nm spectrophotometrically after appropriate dilution with buffer. The Entrapment Efficiency (EE) was determined by using the following empirical relationship. Each determination was performed in triplicate manner.

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Actual drug content (AC)}}{\text{Theoretical drug content (TC)}} \times 100$$

AC - Actual quantity of drug present in the beads

TC - 100% theoretical quantity of drug present in the beads (actual initial dose)

DRUG RELEASE STUDIES

IN VITRO DRUG RELEASE STUDIES[27]

100 mg of drug loaded alginate beads were evaluated for *in vitro* drug release. The study was carried out in the USP XXIV Type I apparatus using 900ml phosphate buffer (pH 7.4) solution and rotated at constant speed (75 rpm) and the temperature of the medium was maintained at 37°±0.5°C for 8 hours. A muslin cloth was tied over the basket to prevent the slippage of beads from the basket. An aliquot of the sample (5ml) was periodically withdrawn at the regular time intervals (0,0.5,1,2,4,6 & 8 hrs)

and an equal volume was replaced with fresh dissolution medium. The test samples were filtered and analyzed spectrophotometrically at 274 nm after appropriate dilution with buffer. The study was performed in triplicate for each batch. The percentage drug released at different time intervals were calculated. The *in vitro* drug release profiles were obtained by plotting the percentage release Vs time in hours.

DISSOLUTION KINETICS OF DRUG RELEASE [50]

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models:

Zero order (Equation 1) as cumulative amount of drug released vs time,

First order (Equation 2) as log cumulative percentage of drug remaining vs time,

Higuchi's model (Equation 3) as cumulative percentage of drug released vs square root of time and

Korsmeyer's (Equation 4) log cumulative percentage of drug released vs. log time

$$C = K_0 t. \qquad \text{(Equation1)}$$

where K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours.

A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

$$\left[\log_c = \log C_0 - kt/2.303\right] \qquad \text{(Equation2)}$$

where C_0 is the initial concentration of drug,

k is the first order constant, and t is the time.

$$Q = Kt^{1/2} \qquad \text{(Equation3)}$$

where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Drug release were plotted in Korsmeyer et al's equation (Equation 4) as log cumulative percentage of drug released vs log time, and the exponent n was calculated through the slope of the straight line.

$$M_t / M_\infty = Kt^n \qquad \text{(Equation4)}$$

where M_t/M_∞ is the fractional solute release,

t is the release time, K is a kinetic constant.

ANALYTICAL METHODS

DEVELOPMENT OF CALIBRATION CURVE FOR ACECLOFENAC

Preparation of Buffers

The phosphate buffer solution of pH 7.4 was prepared as per procedures described in Indian Pharmacopoeia[51] 1996 and the pH was confirmed by using a digital pH meter.

Preparation of aceclofenac stock solution

100mg of aceclofenac was accurately weighed and transferred to 100ml volumetric flask, and it was dissolved in phosphate buffer (pH 7.4) and the volume was made upto 100ml using the buffer which gives 1mg/ml concentration.10ml of the above solution was withdrawn and the volume was made upto 100ml by phosphate buffer to give **100mcg/ml** which will be used as a stock solution.

Preparation of working standard solution

From the stock solution further dilutions were made to obtain (5, 10, 15, 20, 25, 30, and 40mcg/ml) by using phosphate buffer. The absorbance's of the solutions were measured at 274 nm using UV spectrophotometer against blank (phosphate buffer).

The graph was plotted against concentration (µg/ml) vs. absorbance. The details of the solutions prepared were given in the **Table 7.**

TABLE: 7 STANDARD SOLUTION DETAILS

S.No	Volume of stock solutions (100 µg /ml)	Volume of buffer solutions (ml)	Final volume (ml)	Final concentration (µg/ml)
1	0.5	9.5	10	05
2	1.0	9.0	10	10
3	1.5	8.5	10	15
4	2.0	8.0	10	20
5	2.5	7.5	10	25
6	3.0	7.0	10	30
7	4.0	6.0	10	40

STANDARD GRAPH OF ACECLOFENAC

An attempt was made to obtain to conform the λ_{max} value by scanning of the solutions prepared with different solvents were done and reported[27,17] λ_{max} was confirmed as 274 nm.

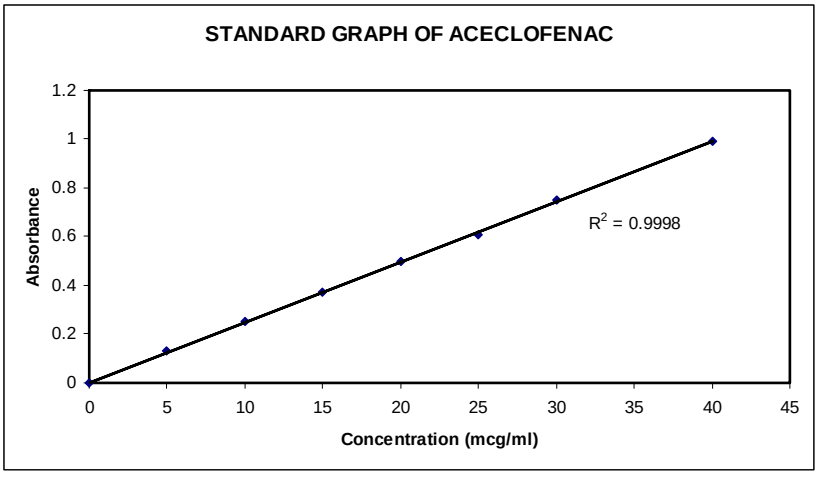
The calibration curve obtained was found to be linear with the selected concentrations and it was reported in **Table 8** and **Fig 4**

It obeys the Beer's-Lambert limit 5 – 30 µg/ml regression equation (Absorbance =0.0024+0.0247 *concentration), the value of correlation co - efficient for aceclofenac was found to be 0.9998. This correlation co - efficient suggest the level of precision of the method.

TABLE: 8 Standard graph of aceclofenac in phosphate buffer pH 7.4

S.No	Concentration (µg/ml)	Absorbance at 274 nm
1	0	0
2	5	0.1305
3	10	0.2496
4	15	0.3713
5	20	0.4987
6	25	0.6108
7	30	0.7507
8	40	0.9923

FIG: 4 Standard graph of aceclofenac with phosphate buffer pH 7.4



Absorbance=A + B*Concentration A=0.0024 B=0.0247

SUMMARY

The current study "**FORMULATION, PHYSICAL CHARACTERIZATION AND *IN VITRO* RELEASE STUDIES OF ACECLOFENAC ALGINATE BEADS PREPARED BY IONOTROPIC GELATION FOR SUSTAINED RELEASE"** was to develop suitable particulate system of aceclofenac for sustained release system by the influence of varying the concentration of sodium alginate, concentration of calcium chloride, different curing time intervals, different cross linking agents and addition of chitosan to calcium chloride were also studied. The results obtained from the above study can be summarized as follows.

- Literatures pertaining to alginate beads, cross linking agents, chitosan and drug aceclofenac were surveyed thoroughly and documented.
- Standard graph was prepared by using phosphate buffer (pH 7.4) and analyzed by UV spectrophotometer at 274 nm. It gives linear with the selected concentrations.
- Optimization of process parameters stirring speed, bore diameter of syringe, drying time were done.
- Alginate beads containing aceclofenac and varying the concentration of sodium alginate, concentration of cross linking agent, different curing time interval, different cross linking agents and addition of chitosan to calcium chloride were prepared by ionotropic gelation and analysed.

COMPATIBILITY STUDIES

IR spectral analysis

The IR spectrum revealed that there was no interaction between the drug and the polymer.

DSC thermogram analysis

The thermogram of the prepared formulation revealed that the drug was uniformly dispersed at the molecular level in the beads.

PHYSICAL CHARACTERIZATION

Particle size and size distribution analysis

- The particle size distribution of each formulation was very well within a narrow size range.
- An increase in the concentration of sodium alginate the average mean diameter of the beads were increased.
- The particle size would have been larger if the same was air dried which may be because of in complete dehydration of the formed beads.
- The size of the beads were increased with addition of chitosan in the cross linking solution. This is probably due to extra coating provided by the adding chitosan.
- No significant variations in particle size of the alginate beads prepared using increased concentrations of cross – linking agent, curing time and different type of cross linking agent.

Scanning electron microscope

- In all formulations**,** the shape of the alginate beads was more or less spherical and the exterior surfaces were rough.

X-Ray Diffraction

- ✍ The X-ray diffraction study exhibited that reduction in both number and intensity of peaks compared to plain aceclofenac indicating the decrease in crystallinity or partial amorphization of the drug in prepared alginate beads.

- ✍ Thus XRD data supports the DSC studies which indicated the decreased crystallinity of drug in the prepared alginate beads.

DRUG CONTENT ANALYSIS

- ✍ Increasing the concentration of sodium alginate resulted in, increase in drug entrapment this is due to decreased drug loss from the highly viscous polymer gel.
- ✍ Increasing the concentration of cross linking agent resulted in, increase in drug entrapment this is due to availability of active calcium binding sites in the polymeric chain.
- ✍ The entrapment efficiency of formulations were slightly decreased with increasing the curing time.
- ✍ The entrapment efficiencies were higher for the formulations prepared with cross – linking agent barium chloride and aluminium sulphate as compared to the beads cross - linked with calcium chloride. This may be due to the extent and apparent cross - linking density in the beads in the presence of Al^{3+} and Ba^{2+}.
- ✍ By the addition of chitosan the drug encapsulation was increased. This was probably due to increased ionic interactions between the carboxylate groups in the alginate and the protonated amine groups in the chitosan.

IN VITRO DRUG RELEASE STUDIES

- Increase in the concentration of sodium alginate the drug release rate becomes more sustained. This probably due to the number of the apparent cross - linking points and density formed within the calcium alginate beads.
- Increased in the concentration of calcium chloride more sustained effect was produced, this may be due to formation of strong rigid gel beads which may reduce the penetration of dissolution medium.
- By using the Ba^{2+} and Al^{3+} in cross - linking solutions more sustained effect was produced compared to calcium alginate beads.
- The release behavior of alginate beads produced by ionic gelation with different cross – linking agents depend upon the valency and size of the cations of the respective cross – linking agent.
- With the addition of chitosan in the cross - linking solution, the release of drug from chitosan alginate beads was very low, because it forms the outer coat.

KINETICS OF DRUG RELEASE

- The results indicated that the drug release from formulation followed the diffusion controlled model as described by Higuchi's square root of time equation.

CONCLUSION

It can be concluded from the above investigation that the proper selection of formulation parameters are important to achieve high entrapment efficiency and to sustained the release of drug from alginate beads. Ionotropic gelation technique can be successfully used for preparation of aceclofenac alginate beads. Aceclofenac releases from the beads were influenced by sodium alginate, calcium chloride concentration. By increasing the polymer and cross linking concentration entrapment efficiency increased and drug release were more sustained effect. And also by the addition of different cross linking agent, chitosan in the cross linking solution can very much alter the drug encapsulation and release characteristics. Effect of curing time on the drug release, encapsulation efficiency was less significant. Therefore, more formulation studies are needed to design the best sustained release formulation.

FUTURE WORK

The study can be extended by putting an effort to increase the entrapment efficiency, release characteristics and standardizing the process variables like temperature, addition of polymers to the cross linking solution, volume of the internal phase, processing time, type of surfactant in the external phase can also be studied and their effect on the size of the beads formed, drug entrapment efficiency, and *in-vitro* and *in-vivo* release studies can also be performed, to standardize a successful formulation.

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ABBREVIATIONS

SR	Sustained Release
SA	Sodium Alginate
CA	Calcium Alginate
NSAID	Non Steroidal Anti Inflammatory Drug
COX	Cyclooxygenase
IP	Indian Pharmocopeia
BP	British Pharmocopeia
Ph Eur	European pharmacopoeia
NF	National Formulary
IR	Infra Red spectrometer
UV/Vis	Ultra Violet /Visible
DSC	Differential Scanning Calorimeter
X-RD	X-Ray Diffractrometer
WHO	World Health Organization
$CaCl_2$	Calcium Chloride
$Al_2(SO_4)_3$	Aluminium sulphate
$BaCl_2$	Barium Chloride

ABSTRACT

The objective of the present study was to microencapsulate the anti-inflammatory drug (aceclofenac) to provide sustained release and minimizing or eliminating drug release in the upper gastro intestinal tract. Alginate beads of aceclofenac were formulated by ionotropic gelation and the variables studied includes the effect of concentration of sodium alginate, concentration of cross linking agent ($CaCl_2$), different curing time intervals, different cross linking agents, and addition of chitosan with $CaCl_2$ were evaluated with respect to particle size, surface characteristics, entrapment efficiency and *in vitro* release behaviors. Infra Red spectroscopic study confirmed the absence of any drug interaction. Differential Scanning Calorimeter (DSC) analysis revealed that the drug was uniformly dispersed in the alginate beads. The mean particle size increases with increasing the polymer concentration and addition of chitosan. The shape of the alginate beads have acceptable sphericity and surfaces were rough which were confirmed by Scanning Electron Microscope photographs. The X-ray diffraction data supports the DSC studies which indicated the decreased crystallinity of drug in the prepared alginate beads. The entrapment efficiency in different formulation varied from 62.18% to 87.96%. The *in vitro* release profiles were also altered significantly by changing various parameters. The kinetic modeling of the release data indicates that aceclofenac released from the alginate release from the alginate beads followed by the Matrix Higuchi model. From the study it can be concluded that aceclofenac could be successfully prepared by ionotropic gelation technique with high entrapment efficiency and prolonged release characteristics.